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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/447,118	05/22/95	BURKLY L	BGP-151CP(D

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ART UNIT	**PAPER NUMBER**
1806 1806	10

DATE MAILED: 03/04/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on Election filed

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 (month(s), ~~or thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the ~~period for~~ response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 1-24 is/are pending in the application.

Of the above, claim(s) 1-9 + 21-24 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 10-20 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____ 4 Sheets

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

– SEE OFFICE ACTION ON THE FOLLOWING PAGES –

1. Claims 1-24 are pending and claims 1-9 and 21-24 have been withdrawn from further consideration by the examiner, under 37 CFR 1.142(b) as being drawn to a non-elected invention. Claims 10-20 are currently under prosecution.

2. The response filed December 13, 1996 (Paper No. 7) to the restriction requirement of November 13, 1996 (Paper No. 6) has been received. Applicant has elected Group III, claims 10-14 for examination with traverse. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)). However, in reviewing the claims and upon reconsideration of the restriction requirement it has been deemed that claims 15-20 should properly belong to the elected Group III, claims 10-14, and therefore a revision of the restriction requirement follows:

3. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

Group I. Claims 1-9 are a method for the prevention of insulin dependent diabetes classified in Class 424, subclasses 130.1 and 141.1.

Group II. Claims 10-20 drawn to a method of treating diabetes classified in Class 424, subclasses 130.1 and 141.1, and Class 514, subclass 2.

Group III. Claim 21-22 are drawn to a chimeric molecule classified in Class 530, subclass 187.3

Group IV. Claims 23-24 are drawn to a method of treating a subject at risk for a disorder classified in Class 424, subclass 183.1.

4. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I, II, and IV are materially distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success.

The inventions of Groups III and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (i) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the chimeric molecule can be used for a materially different process, i.e. for affinity chromatography.

The inventions of Groups III and IV are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (i) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the chimeric molecule can be used for a materially different process, i.e. for affinity chromatography.

The inventions of Groups III and I are not related because the chimeric molecule is not used in the method of Group I.

5. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

6. Group II is further subject to election of a single disclosed species.

Claims 10 and 11 are generic to a plurality of disclosed patentably distinct species comprising methods for treatment of diabetes comprising administering: (1) an antibody (claims 15 and 28); (2) a polypeptide (claims 12-14); and, (3) a small molecule (claim 19). Claims 16 and 17 are improper Markush groups dependent upon Claim 10 and will be examined with the elected species.

7. Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

8. A telephone call was made to Louis Myers (617)-227-7400, on February 27, 1997 to request an oral election to the above restriction requirement, a provisional election was made with traverse to prosecute the invention of Group II, claims 10-20 and species 2 claims 12-14. Affirmation of this election must be made by applicant in responding to this Office action.

9. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an

inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

10. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

Oath/Declaration

11. The oath or declaration is defective. A new oath or declaration in compliance with 37 C.F.R. § 1.67(a) identifying this application by its Serial Number and filing date is required. See M.P.E.P. §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration in a continuation-in-part application filed under the conditions specified in 35 U.S.C. § 120 which discloses and claims subject matter in addition to that disclosed in the prior copending application, acknowledges the duty to disclose material information as defined in 37 C.F.R. § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

Specification

12. The attempt to incorporate subject matter into this application by reference to US Application Serial No.08/376,372 on page 8 is improper because material essential to the practice of the invention can be incorporated by reference only if

the reference is a US patent or an allowed US application in which the issue fee has been paid. See In re Fouche 169 USPQ 429:439 F.2d 1237 (CCPA 1971).

Drawings

13. The drawings are objected to because of the following informalities:

(a) Figure 5 recites PBS->Y but PBS->Y is not defined either on the figure or in the Brief Description of the drawings. Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112: "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

15. The specification is objected to and claim 11 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to monoclonal antibody HP1/2 and fragments thereof used in a method of treating diabetes.

It is unclear if a cell line which produces an antibody having the exact structural and chemical identity of HP1/2 is known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without

access to a hybridoma cell line producing monoclonal antibody HP1/2, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, HP1/2. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the antibody species, HP1/2. If a deposit has been made under the

provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

16. The specification is further objected to under 35 USC 112, first paragraph, and Claims 10, 11 and 15-18 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating diabetes by administering "fragments of antibodies" to VLA4 or polypeptides which bind to VLA4 or small molecules.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The specification provides no guidance on or exemplification of how to use the claimed immunotherapeutic method for successful treatment of any diabetes other than type I diabetes in NOD mice.

Further, the specification discloses data based solely on an adoptive diabetes transfer experiment in NOD mice. The spleen cells which were transferred to the NOD mice were treated with the R1-2 mAb which is an antibody specific for VLA4. The antibody was then administered to the transfer model for two weeks in order to coat the VLA4 positive cells. In general, data such as that disclosed in the specification, cannot be extrapolated to predict human efficacy *in vivo* as it would be impossible to duplicate the saturation of spleen cells with the desired antibodies prior to onset of the disease. It would appear that although the NOD model is effective in studying the onset of diabetes, it is not sufficiently correlative of therapeutic utility. Further, the art does not recognize a reliable correlation between mouse animal model data such as those presented in the specification and human efficacy. Osband et al. (Immunol. Today, 11:193-195, 1990) teach on pages 193-194 that while the response of animals to chemotherapy, radiation and surgery is generally predictive of their effect in human patients, this is not the case with immunotherapy. This is due in part, to the fact that animal models do not fully mimic the biology of human patients. Harris (Tibtech, 11:42-44, 1993) teaches that "there is widespread acceptance that there is little future for the use of rodent mAbs in human therapy." Harris does however, say that humanized antibodies show some potential, but is unwilling to definitively commit to this view until further "clinical" data has been presented and evaluated (see whole article). In view of the comtemporary knowledge in the art of the general lack of successful application of monoclonal antibody-based therapy methods for treatment of human diseases and of the

limited predictive value of animal results for efficacy in humans, as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

17. The specification is further objected to under 35 USC 112, first paragraph, and Claims 10-14 and 16-17 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating diabetes by administering "fragments of antibodies" to VLA4 or polypeptides which bind to VLA4 or small molecules.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The specification provides no guidance on or exemplification of how to use the claimed polypeptide therapeutic method for successful treatment of any diabetes other than type I diabetes in NOD mice. The specification states on Page 21 that the adoptive transfer experiment described for the antibodies was repeated successfully with the VCAM 2D-IgG. The specification does not address the pharmacokinetic properties of VLA4 binding peptides. At the time of filing of the instant application it was known that different proteins and pepides exhibited not only different clearance capabilities but different cross reactivities. Further, because *in vivo* administration of a polypeptide may involve different routes, dosages, schedules, etc., and also exposes the polypeptide to complex environments including blood

cells and proteins, and also diverse organs such as the liver, lungs, kidney, and spleen, the fate and activity of the polypeptide is unpredictable regarding its ability to bind VLA-4 *in vivo* in and can't be predicted in humans because animal models do not fully mimic the biology of human patients.

In view of the contemporary knowledge in the art of the limited predictive value of animal results for efficacy in humans, as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

18. The specification is further objected to under 35 USC 112, first paragraph, and Claims 10, 11, 16, 17 and 19 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating diabetes by administering "fragments of antibodies" to VLA4 or polypeptides which bind to VLA4 or small molecules.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The specification provides no guidance on or exemplification of how to use the claimed small molecule therapeutic method for successful treatment of any diabetes. The specification defines small molecules as those that mimic the action of anti-VLA-4 antibodies in the treatment of diabetes (p. 4, lines 36-37) and carbohydrates (p. 4, line 15) but does not give guidance as to administration of a small molecule or which

specific small molecules would mimic the action of anti-VLA-4 antibodies in the treatment of diabetes, further, the specification does not address the pharmacokinetic properties of VLA4 modulating small molecules. At the time of filing of the instant application it was known that small molecules exhibited not only different clearance capabilities but different cross reactivities. Further, because *in vivo* administration of small molecules may involve different routes, dosages, schedules, etc., and also exposes the small molecules to complex environments including blood cells and proteins, and also diverse organs such as the liver, lungs, kidney, and spleen, the fate and activity of the small molecules is unpredictable regarding their ability to mimic the action of anti-VLA-4 antibodies *in vivo*.

In view of the unpredictability pertaining to the ability of small molecules to mimic the action of anti-VLA-4 antibodies *in vivo* as discussed above as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

19. The specification is further objected to under 35 USC 112, first paragraph, and Claims 10-19 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating diabetes by administering "fragments of antibodies" to VLA4 or polypeptides which bind to VLA4.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant

invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The claims as drawn read on the treatment of diabetes in all stages of the disease. The specification provides no exemplification of how to use the claimed antibodies and polypeptides for the treatment of diabetes once damage has been done and the Islet cells are dead. The mechanism of action of treatment by the claimed antibodies and polypeptides is blockade of binding of VCAM-1 to VLA-4 which prevents the adhesion of leukocytes to inflamed endothelium, protecting Islet cells from damage and cell death, thus the efficacy of the instant method for treatment of diabetes, when the Islet cells are already dead would be highly unpredictable.

In view of the unpredictability pertaining to the efficacy of treating diabetes with the instant invention when the Islet cells are already dead as discussed above as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

20. The specification is further objected to under 35 USC 112, first paragraph, and Claims 10-19 are rejected under 35 USC 112 first paragraph as failing to provide sufficient guidance to enable one skilled in the art to use a method of treating diabetes by administering "fragments of antibodies" to VLA4 or polypeptides which bind to VLA4 or a small molecule.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make/use the instant

invention commensurate with the scope of the claims. The specification on page 4, lines 12-17, contemplates the use of the claimed invention for the treatment of diabetes in humans. The claims as drawn read on an all antibodies, polypeptides and small molecules that bind to all VLA-4 positive cells. Jabukowski et al (J. Immunol, 1995, 155: 938-946) specifically teach that monoclonal antibodies R1-2 and PS/2 bind to all alpha 4 positive cells *in vitro* and *in vivo* infusion and reports a VCAM-Ig fusion polypeptide that is specific for activated receptors, preventing the binding of VLA-4 to inflamed tissues required for the inflammatory response, sparing the majority of circulating and tissue resident cells (p. 943, para 3). Further, Jabukowski et al teach that lymphocytes, monocytes, macrophages, eosinophils and basophils adhere to VCAM-1 through VLA-4 (p. 938). The specification gives no guidance or exemplification of how to use the claimed method of administering antibodies, polypeptides or small molecules to specifically target cells, in humans, involved with the inflammation related pathogenesis of diabetes. Treatment of diabetes with the administration of the claimed antibodies, polypeptides or small molecules that bind to all VLA-4 positive cells would perturb the complex regulatory network involving these cell types and eliminate binding of VLA-4 positive cells to VCAM-1 positive tissues. Elimination of suppressor T cell function would be expected to interfere with suppressor T cell functions, for example, the inhibition of cytotoxic T cells that mediate the pathogenesis of diabetes. Thus, the effects of the treatment by the instant method would be highly unpredictable and could exacerbate rather than treat, diabetes.

In view of the unpredictability pertaining to the effects of treatment by the instant method as discussed above as well as the lack of sufficient guidance in the specification, one of skill in the art would be forced into undue experimentation in order to use the invention, as claimed.

21. Claims 10-19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-19 are indefinite because claim 10 recites an improper Markush group. MPEP 706.03(y) provides that the materials set forth in a Markush group ordinarily must belong to a recognized physical class or chemical class or to an art-recognized class. When the Markush group occurs in a claim reciting a process or a combination it is sufficient if the members of the group are disclosed in the specification to possess at least one property in common which is responsible for their function in the claimed relationship and it is clear from their very nature or from the prior art that all of them possess this property.

The members of the Markush groups recited in claim 10 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 1 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the polypeptide acts by competing with endogenous polypeptides or small molecules to prevent complex formation. The above embodiments should be set out as

separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.

Claims 10-19 are indefinite for because claim 10 is in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

Claims 10-19 are indefinite because claim 1 recites the phrase "or small molecule". It is not clear what is meant by a small molecule, for example, is it a protein, a peptide, Calcium, or magnesium?

Claims 10-19 are indefinite because claim 1 recites the phrase "or combinations of any of the foregoing". It is not clear which or how many combinations of antibodies, polypeptides or small molecules are claimed for patent protection.

Claim 11 is indefinite because claim it recites an improper Markush group. The members of the Markush groups recited in claim 11 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 11 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the VCAm-1 or fibronectin polypeptides act by competing with endogenous VCAM-1 or fibronectin polypeptides to complex formation. The above embodiments should be set out as separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.

Claim 11 is indefinite for being in improper Markush format.The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

Claim 11 is indefinite because it recites the phrase "or small molecules". It is not clear what is meant by small molecules, for example, are they proteins, a peptides, Calcium, or magnesium?

Claim 11 is indefinite because it recites the phrase "small molecules". It is not clear whether one small molecule or many small molecules bind to the VCAM-1 or fibronectin binding domain of VLA-4.

Claim 15 is indefinite because it recites the phrase "a plurality of...monoclonal antibodies". It is not clear if it is one antibody or a group of different antibodies that are binding to VLA-4.

Claim 16 is indefinite because claim it recites an improper Markush group. The members of the Markush groups recited in claim 16 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 11 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the VCAm-1 or fibronectin polypeptides act by competing with endogenous VCAM-1 or fibronectin polypeptides to complex formation. The above embodiments should be set out as separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.

Claim 16 is indefinite for being in improper Markush format.The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

Claim 16 is indefinite because it is unclear whether the compositions to be administered, that is antibody, polypeptide or small molecule, are to be administered separately or in combination.

Claim 17 is indefinite because claim it recites an improper Markush group. The members of the Markush groups recited in claim 17 do not belong to a recognized class nor do they function by a common mechanism to treat or prevent diabetes. The Markush groups of claim 11 recite antibodies which are immunoreactive with the gamma 4 subunit of VLA-4 which act by complexing with the gamma 4 subunit of VLA-4 to prevent complex formation and the VCAm-1 or fibronectin polypeptides act by competing with endogenous VCAM-1 or fibronectin polypeptides to complex formation. The above embodiments should be set out as separate claims. The mechanism of action of a small molecule is unclear because of the indefinite language used.

Claim 17 is indefinite for being in improper Markush format.The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. See MPEP 706.03(Y).

Claim 17 is indefinite because it is unclear whether the compositions to be administered, that is antibody, polypeptide or small molecule, are to be administered separately or in combination.

Claim 18 is indefinite because the word "fragement" is misspelled.

Claim 18 is indefinite because it recites the phrase "period of 1-14 days". It is not clear if 2, 3, 6, or 12 days are being claimed for patent protection.

Claim 19 is indefinite because it recites the phrase "small molecule". It is not clear what is meant by a small molecule, for example, is it a protein, a peptide, Calcium, or magnesium?

Claim 19 is indefinite because it recites the phrase "period of 1-14 days". It is not clear if 2, 3, 6, or 12 days are being claimed for patent protection.

Claim 20 is indefinite because it recites the phrase "consisting essentially of". The specification does not define the phrase. Does "consisting essentially of" include polyclonal antibodies, polypeptides and small molecules? Rejection of the claim can be obviated by amending the claim to delete the phrase "consisting essentially of" and replacing it with "comprising".

Double Patenting

22. Claims 10, 11, 15-17 and 20 are provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 10-11, 12-14 and 16 of copending application Serial No. 08/447,098. This is a *provisional* double patenting rejection since the conflicting claims have not in fact been patented.

23. The non-statutory double patenting rejection, whether of the obviousness type or non-obviousness type, is based on a judicially created doctrine grounded

in public policy (a policy related in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 438, 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b)

1. Claim 18 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 13 of copending application Serial No. 08/447,098. Although the conflicting claims are not identical, they are not patentably distinct from each other because the administration of composition dosage, of about 0.1 to about 10 mg/kg of the susceptible body weight would be expected by one of skill in the art to provide a plasma level of antibody or antibody fragment of at least 1 microgram/ml over a period of 1-14 days.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claim 19 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14 of copending application Serial No. 08/447,098. Although the conflicting claims are not identical, they are not patentably distinct from each other because the limitations of claim 19 of the instant application are within the scope of claim 14 of Serial No. 08/447,098.

This is a *provisional* obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

26. Claim 20 is rejected under 35 U.S.C. § 102(b) as being anticipated by Elices et al. (Cell 1990, IDS Item BD) or Issekutz (Journal of Immunology 1991, IDS Item BR).

The claim is drawn to a pharmaceutical composition comprising an antibody which recognizes VLA4, wherein the composition is in a pharmaceutically acceptable carrier and is able to prevent the onset of diabetes.

First it should be noted that the intended use clause int he claim has no patentable weight on the examination of the product which in this case is an anti-VLA4 antibody. Second, in general, any buffer which contains the monoclonal antibody, eg. water or PBS etc is a pharmaceutically acceptable carrier.

Issekutz teaches the use of TA-2, an Ig Kappa antibody specific for VLA4 for inhibiting lymphocyte migration in vivo (see materials and methods and figure 1).

Elices teaches anti-VLA4 antibodies which inhibit ICAM interactions.

The product of the claims is anticipated by the anti-VLA4 antibodies of the prior art.

27. No claims allowed.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached at (703) 308-2731. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Susan Ungar

February 27, 1997

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800